March 1956

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Disease-a-Month

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Antibiotic Therapy

HARRY F. DOWLING

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had his training at George Washington University School of Medicine, where he received his M.D. After residencies at Johns Hopkins University and Harvard Medical School, he returned to his alma mater, where he became Clinical Professor of Medicine and Chief of the George Washington Medical Division of Gallinger Memorial Hospital. In 1950 he came to the University of Illinois College of Medicine, and in 1951 was appointed Professor of Internal Medicine and Head of the Department, and Chief of Medicine at the Research and Educational Hospitals. Dr. Dowling's field of research has been concerned primarily with infectious diseases, including the methods of action of serum, sulfonamides and antibiotics. He has written numerous articles and several books concerned with various aspects of his specialty.

AN ANTIBIOTIC is a chemical substance of microbial origin that possesses antimicrobial activity. Since 1941, when penicillin was first given to patients, antibiotics have become one of the most important and frequently used groups of drugs in the practitioner's armamentarium. Some realization of the large amounts of antibiotics that are used can be obtained from the fact that approximately one-half the patients admitted to hospitals today receive antibiotics at some time during their stay, and from the quantities of antibiotics produced in the United States of America. During the year 1953 these were: penicillin, 378 tons; streptomycin and dihydrostreptomycin, 187 tons; and the tetracyclines and chloramphenicol, over 200 tons.

THE VARIOUS ANTIBIOTICS AND RECOMMENDED DOSES

We shall confine ourselves here to a consideration of the antibiotics that are available for systemic use, ignoring those that are

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TABLE 1.—Antibiotics and Use against Various Micro-Organisms

Antibiotic	Route of Administration	Dosages for Adults	Used for infections caused by:
Penicillin			
Benzylpenicillin (penicillin G or "regular" penicillin)	Oral I.M., I.V.	see Table 2	*Gram positive cocci*[a] *Gonococcci* *Treponema pallidum* Meningococci
Procaine penicillin in aqueous solution in oil	I.M.		
Benzathine penicillin	I.M.		
Phenoxymethyl-penicillin (penicillin V)	Oral		
Streptomycin Dihydrostreptomycin	I.M.	1 Gm. twice a week 2–4 Gm./day	*Myco. tuberculosis* Gram-negative rods
Tetracyclines			*Coliforms*
Chlortetracycline	Oral	2 Gm./day	*H. influenzae*
Oxytetracycline	I.M.	10mg./kg. body weight at 12-hr. intervals	*H. pertussis* *Shigellae* *Rickettsiae*
Tetracycline	I.V.	1–2 Gm./day	*Certain large viruses* *Gram-positive cocci* *Klebsiella (Friedländer's bacillus)*
Chloramphenicol	Oral	4 Gm./day	*Salmonellae*
	I.M.	10 mg./kg. at 12-hr. intervals	*Proteus* *Klebsiella*
	I.V.	2–3.5 Gm./day	Other gram-negative rods Staphylococci resistant to other antibiotics
Erythromycin **Carbomycin**	Oral I.V.	2 Gm./day 1 Gm. every 8 hr.	Gram-positive cocci (especially staphylococci resistant to other antibiotics)

TABLE 1 *(Cont.)*

Antibiotic	Route of Administration	Dosages for Adults	Used for infections caused by:
Bacitracin	I.M.	200 units/kg. body weight every 6 hr.	Staphylococci resistant to other antibiotics
Polymyxin	I.M.	1 mg./kg. every 12 hr.	*Pseudomonas*
Streptonivicin† Cathomycin†	Oral	2 Gm./day	Staphylococci resistant to other antibiotics
Nystatin	Oral	500,000 units every 6 hr.	Monilia

*When an antibiotic is the drug of choice, the organism is in italics.
†See footnote, p. 7.

used only locally. Table 1 lists these antibiotics according to their generic names. Confusion often arises as a result of the large number of proprietary names that have been given to the commercial preparations of the antibiotics available for administration. It is important, therefore, that the physician order the preparation he desires by its generic (or pharmacopeial) name.

Penicillin.—When penicillin is administered by the oral route, either penicillin G (benzylpenicillin) or penicillin V (phenoxymethylpenicillin) may be used. They have the same effect on bacteria, but penicillin V is more stable in the presence of gastric acidity, and the concentrations reached in the blood are approximately twice those obtained with penicillin G. For this reason penicillin V is to be preferred for oral administration if it is used alone. Concentrations similar to those obtained with penicillin V, however, can be obtained by the use of penicillin G, plus 0.5 Gm. of probenecid (Benemid) administered by mouth at six hour intervals. Probenecid acts by delaying the renal excretion of penicillin.

When penicillin is given intramuscularly, the physician should be careful to distinguish between penicillin G, which will give appreciable concentrations in the blood for a few hours, and

repository preparations. The latter include procaine penicillin in aqueous solution, the administration of which is followed by detectable blood concentrations for 12–24 hours; procaine penicillin in oil with aluminum monostearate, which produces detectable concentrations for two to four days, and benzathine penicillin, which gives low blood levels for from one to four weeks, depending upon the dose administered.

When penicillin is given by the intravenous route, only crystalline penicillin G is used. Probenecid may be given orally to double or triple the concentration of penicillin in the blood when the antibiotic is administered intramuscularly or intravenously, as well as when it is given orally.

Penicillin is the antibiotic of choice for infections caused by gram-positive cocci: pneumococcus and group A beta hemolytic streptococcus; also the staphylococcus if the growth of the particular strain is inhibited by penicillin. Infections caused by the gonococcus and Treponema pallidum are preferentially treated with penicillin. Penicillin may be used also in meningococcic infections, but since the large doses required are expensive, the sulfonamides, which are just as effective, are preferred. Among the gram-negative rods, some strains of Proteus mirabilis are sensitive to penicillin.

STREPTOMYCIN; DIHYDROSTREPTOMYCIN. — These have the same antibacterial activity and will therefore be considered together. They are administered intramuscularly for tuberculosis, and occasionally for infections caused by gram-negative rods, when these are inhibited by streptomycin and not by other antibiotics. These antibiotics are used orally only for purposes of temporarily suppressing the growth of the gastrointestinal flora, since they are not absorbed to any appreciable extent from the alimentary tract.

TETRACYCLINES.—The three tetracyclines are listed together because their actions against micro-organisms are practically identical. They are the drugs of choice in infections caused by organisms of the coliform group (escherichia, aerobacter, paracolobactrum), Hemophilus influenzae, Hemophilus pertussis, the shigellae, the rickettsiae and the viruses causing psittacosis and lymphopathia venereum. They may also be of value in primary atypical pneumonia. They can be used in infections caused

by the gram-positive cocci and klebsiella (the Friedländer bacillus) also.

CHLORAMPHENICOL is the drug of choice for typhoid fever and other salmonella infections and is more likely to be effective in proteus infections than any other antibiotic. It is used in infections caused by other gram-negative rods and the staphylococci when the strain causing the infection is resistant to other antibiotics. Its use is not recommended if any other antibiotic is equally effective because it occasionally produces a blood dyscrasia.

ERYTHROMYCIN; CARBOMYCIN.—These are listed together in Table 1, because they have the same antibacterial action. The blood concentrations of carbomycin are not so high as those obtained with erythromycin, and even in large doses the former is relatively ineffective in human infections. Accordingly, carbomycin is rarely used clinically and is not recommended. Erythromycin has been shown to be as effective as penicillin in streptococcic sore throat (including scarlet fever). It should be used instead of penicillin in these and other infections caused by group A streptococci, such as erysipelas, otitis media, puerperal sepsis, pneumonia, and so forth, when the patient is hypersensitive to penicillin. It may also be used instead of penicillin in order to minimize the possibility of patients becoming hypersensitive to penicillin. It is especially useful in infections caused by staphylococci that are resistant to penicillin and the tetracyclines.

BACITRACIN is used occasionally in severe infections caused by staphylococci that are resistant to all of the other antibiotics. POLYMYXIN is the drug of choice for serious pseudomonas (pyocyaneus) infections. The use of both of these drugs is limited because they may cause renal damage when administered parenterally in large doses.

STREPTONIVICIN;* CATHOMYCIN.*—These two newer antibiotics have been found to possess an identical antibacterial spectrum, because invariably when a strain of bacteria is inhibited in vitro by one of these antibiotics it is inhibited by the other also. Apparently they are similar in chemical structure also. Their use is

*ADDENDUM: The generic name of this compound is now novobiocin. It is being produced as albamycin by the Upjohn Company, and as cathomycin by Sharp & Dohme, Division of Merck & Co., Inc.

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recommended in those staphylococcic infections in which the organisms are resistant to other antibiotics.

NYSTATIN has been found to be effective in some clinical infections caused by monilia (candida).

DOSAGE

PENICILLIN.—Recommended doses of penicillin are listed in Table 2. Infections that are easily controlled by penicillin are

TABLE 2.—RECOMMENDED DOSES OF PENICILLIN

PREPARATION	ROUTE	TYPE OF INFECTION	
		Easily Controlled	Controlled with Difficulty
Benzylpenicillin (penicillin G)	Oral	400,000 units 3 times a day	Not recommended
	I.M.	100,000 units every 4 hr., or 300,000 units every 12 hr.	1–2 million units every 2 hr.
	I.V.	Not recommended	10–80 million units/day by continuous infusion
Procaine penicillin	I.M.	300,000 units/day (in oil)	300,000–600,000 units every 12 hr. or every 8 hr. (in aqueous suspension)
Benzathine penicillin	I.M. For prophylaxis only	600,000 units/wk. 1,200,000 every 4 wk.	Not recommended
Phenoxymethylpenicillin	Oral	200,000 units 3 times a day	Not recommended

pneumococcic pneumonia, streptococcic sore throat (including scarlet fever), erysipelas, superficial staphylococcic infections, such as abscesses and furuncles, and gonococcic urethritis. Infections that are controlled with difficulty are meningitis, arthritis

or endocarditis caused by any of the aforementioned organisms, and infections caused by staphylococci that are relatively resistant to penicillin. Syphilis responds well, but treatment must be carried out for a longer period of time.

When penicillin G is given orally it must be taken at least one-half hour before a meal and at least two hours after a meal. Only one-half the suggested dose need be given if probenecid is given concomitantly in doses of 0.5 Gm. every six hours.

Penicillin V can be given without reference to meals, since it is not destroyed by the hydrochloric acid in the gastric juice. Furthermore, it can be prescribed in half the dose that would be required if penicillin G were used. Whenever larger doses of penicillin are given, either by frequent intramuscular injections or by continuous intravenous infusions, probenecid may be added to the regimen and the penicillin doses halved.

When relatively low blood levels are all that are needed, repository preparations of penicillin may be given, such as procaine penicillin in oil or benzathine penicillin, so as to increase the time between injections. Procaine penicillin in aqueous suspension may be given in larger doses at 12- or 8-hour intervals, but if higher concentrations are required than this regimen will supply, a change to penicillin G is recommended, since more frequent injections of procaine penicillin would be tolerated with difficulty. Benzathine penicillin finds its chief uses in the treatment of syphilis, when 600,000 units may be given once a week, and in the prophylaxis of streptococcic infections, when a single injection of 1,200,000 units need be given only once every four weeks.

Doses of penicillin for children and adults are essentially the same, except that they should be halved for children under 1 year of age and halved again for newborn infants.

Recommended doses for the other antibiotics are shown in Table 1.

STREPTOMYCIN OR DIHYDROSTREPTOMYCIN may be administered in doses of 1 Gm. twice a week in cases of pulmonary tuberculosis. They are always combined with isoniazid or para-aminosalicylic acid to delay the appearance of resistant strains. When streptomycin is given for more acute infections, the dose varies from 2 to 4 Gm. a day, administered in divided doses at 6-hour intervals.

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Such a regimen should not, however, be continued for more than a week or two unless absolutely necessary, since eighth nerve damage is almost certain to result from prolonged therapy. Comparable doses are given to children on the basis of body weight.

TETRACYCLINES.—The dosage regimen is the same for all of the tetracyclines. When the oral route is used, 0.5 Gm. should be given at 6-hour intervals. In the case of tetracycline, an initial dose of 1 Gm. is advisable. Intramuscular injections can be given in the case of tetracycline, although they are somewhat painful. Oxytetracycline appears to be tolerated better on intramuscular injection. The dose is 10 mg. per kilogram of body weight at 12-hour intervals. In serious infections, and especially in meningitis until the patient has become rational and fever has decreased, the intravenous route should be used. The dose is 0.5 Gm. for adults and 7 mg. per kilogram of body weight for children at 6–12-hour intervals.

CHLORAMPHENICOL is given orally in doses of 1 Gm. at 6-hour intervals. An initial dose of 2–4 Gm. has been recommended. Proportional doses should be given to children on the basis of body weight. Intramuscularly, it may be given in doses of 10 mg. per kilogram of body weight at 12-hour intervals. Intravenous doses are calculated on the basis of 50 mg. per kilogram of body weight per 24-hour period, divided into three or four doses and administered at 6–8-hour intervals.

ERYTHROMYCIN should be given orally in doses of 400–500 mg. at 6-hour intervals; comparable amounts are given to children on the basis of body weight. It is administered intravenously in doses of 1 Gm. at 8-hour intervals.

CARBOMYCIN is not recommended for clinical use.

BACITRACIN and POLYMYXIN are reserved for serious infections, because of possible nephrotoxic effects and the upper limits of dosage should be sharply delimited for the same reason. Bacitracin should be given intramuscularly in doses of 200 units per kilogram of body weight at 6-hour intervals. Polymyxin is administered intramuscularly also, in doses of 1 mg. per kilogram at 12-hour intervals, with the upper limit of 2.5 mg. per kilogram per day.

STREPTONIVICIN; CATHOMYCIN.—The optimal dose of these new agents has not been definitely determined as yet, but 0.5 Gm.

by mouth at 6-hour intervals appears to be satisfactory for adults, and comparable doses according to body weight for children.

NYSTATIN is administered orally in doses of 500,000 units at 6-hour intervals.

EFFECTIVENESS OF ANTIBIOTICS IN VARIOUS INFECTIONS

Having considered the various antibiotics that are available for use, I should like to take an over-all view of the results that we may expect when these antibiotics are used in infections. This can be visualized as a war of men against microbes (Fig. 3). The antibiotics and other chemotherapeutic agents have supplied man with heavy artillery which has enabled him to drive back the enemy who have encroached upon the "State of Man's Health" for centuries. Figure 3 shows the present-day battle line, from which it is evident that our success in pushing back the enemy has varied according to the sector involved. We have made our greatest advances in sector III. The micro-organisms in this sector are sensitive to one or more antibiotics and have not developed resistance. They include pneumococci, beta streptococci, meningococci, gonococci and Hemophilus influenzae, the shigellae and the treponemata of syphilis and yaws.

With proper antibiotic treatment the case fatality rate in pneumococcic pneumonia can be reduced to 5 per cent; in pneumococcic meningitis to 15 per cent, and in scarlet fever to 1 per cent or less. Practically every patient with gonococcic urethritis, shigella dysentery or primary or secondary syphilis can be cured completely if the physician is consulted promptly and appropriate therapy is used. The case fatality rate from meningococcic meningitis is between 5 and 10 per cent, and of meningitis caused by Hemophilus influenzae less than 5 per cent.

PNEUMOCOCCIC INFECTIONS.—Pneumococcic pneumonia can be treated with a single injection of 300,000 units of procaine penicillin, in aqueous suspension or in oil, each day until the temperature has remained at practically normal levels for three days. If desired, tetracycline can be substituted in doses of 0.5 Gm. by mouth at 6-hour intervals, or comparable doses for children on the basis of body weight. The temperature usually

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falls within 24–48 hours, although occasionally this may not occur until 72–96 hours.

Pneumococcic meningitis responds best to massive systemic therapy with penicillin. Intramuscular injections of 1,000,000 units of crystalline penicillin G at 2-hour intervals may be given, or continuous intravenous injection of 10,000,000 units of penicillin a day. These doses should be halved for infants. In our experience, intrathecal injections of penicillin are not necessary and introduce the possibility of irritation of the meninges and spinal cord at the site of injection, as well as causing discomfort to the patient.

STREPTOCOCCIC INFECTIONS.—Streptococcic sore throat, scarlet fever and erysipelas respond very well to penicillin. Therapeutic concentrations of the drug should be maintained in the blood for 10 days in order to prevent a recurrence. This may be achieved by the intramuscular administration of 300,000 units of aqueous procaine penicillin each day, or 300,000 units of procaine penicillin in oil intramuscularly on alternative days, or 600,000 units of benzathine penicillin repeated in 5–7 days. Oral therapy is also satisfactory in doses of 200,000 units of phenoxymethyl penicillin (penicillin V), or 200,000 units of penicillin G with 0.5 Gm. of probenecid, or 400,000 units of pencillin G. The indicated dose of any of these oral preparations is given three times a day.

MENINGOCOCCIC INFECTIONS.—Meningococcic meningitis is best treated with sulfonamides—sulfadiazine, sulfisoxazole or triple sulfonamides. Treatment should always be started by the intravenous route. The dose is 5 Gm. initially, followed by 2 Gm. at 8-hour intervals for adults. For children, 1–1½ gr. per pound of body weight is given during each 24-hour period. One-half of this is administered at the start of therapy and one-third at each 8-hour interval thereafter. The same doses are administered to children by the oral route, except that one-sixth of the 24-hour dose is given at 4-hour intervals. When adults are changed to the oral route, they should be given 1 Gm. at 4-hour intervals. The change to oral therapy is made after the temperature falls and the patient has become oriented. Therapy should be continued for one week after the temperature has fallen to normal or nearly normal level.

Penicillin may be used in meningococcic meningitis if desired, although it is more difficult to administer and more expensive than sulfonamides and no more effective. It must be given in large doses, as outlined earlier for pneumococcic meningitis.

The Waterhouse-Friderichsen syndrome is discussed in the section on therapy with hormones and antibiotics (p. 34).

GONOCOCCIC INFECTIONS.—Penicillin is the drug of choice here also. A single dose of 300,000 units of procaine penicillin in aqueous solution or in oil is usually sufficient to cure acute urethritis. In salpingitis, 600,000 units of aqueous procaine penicillin a day for a week or 10 days should be sufficient.

If a patient with acute urethritis is hypersensitive to penicillin, one of the tetracyclines may be given in two doses of 1 Gm. each, six hours apart, or a single dose of 2 Gm. of erythromycin may be given instead. The patient with salpingitis who is hypersensitive to penicillin should receive 0.5 Gm. of tetracycline or of erythromycin at 6-hour intervals for a week or 10 days.

In gonococcic arthritis, 600,000 units of aqueous procaine penicillin every 12–24 hours may be needed, depending on the extent and severity of the disease. This therapy should be continued until all evidences of the infection have subsided.

HEMOPHILUS INFLUENZAE MENINGITIS.—This may be treated with chloramphenicol or with one of the tetracyclines. Tetracycline is given intravenously in doses of 7 mg. per kilogram of body weight, at 6-hour intervals at first. As the child improves, the intervals may be lengthened to 8 hours and then to 12 hours. When the child is definitely better (usually after three days or more) 7 mg. per kilogram can be given by mouth at 6-hour intervals.

Chloramphenicol is given in doses of 50–100 mg. per kilogram per day, divided into four doses administered intravenously at 6-hour intervals. Oral therapy is given later in the same doses. Therapy should be continued for one week after the temperature has reached approximately normal limits.

PERITONITIS.—Peritonitis following the rupture of a viscus responds dramatically to intravenous injections of tetracycline in doses of 0.5 Gm. at 6–12-hour intervals; and comparable doses on the basis of body weight for children. Another satisfactory regimen consists of crystalline penicillin G in doses of 10,000,000

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units a day or more, by continuous intravenous infusion, plus 1 Gm. of streptomycin intramuscularly at 12-hour intervals.

The organisms in sector IV respond almost as well to antimicrobial agents, except that there is a tendency for relapses to occur. These include infections with the Salmonella typhosa (the typhoid bacillus) and other salmonellae, and brucellosis and the rickettsial diseases. I have called these relapses guerrilla warfare because the enemy is easily conquered a second time by the same weapons; in other words, by the same doses of antibiotics as were originally used. Resistant forms of the micro-organisms do not appear in the interim. Why these organisms behave in this particular way to antibiotics is not certain. The most likely explanation is that, after the bacteremia has been cleared, the micro-organisms remain within certain cells, particularly those of the reticuloendothelial system, where they are more or less protected from antibiotics. Thus, they are not eradicated completely, but at the same time resistant forms do not appear. If, however, the organisms again start up an infection outside the cells, so that they can be reached by antibiotics, the infection can be controlled by doses that are no larger than those used in the initial infection.

SALMONELLA INFECTIONS.—Typhoid fever and other salmonella fevers are best treated with chloramphenicol. The dose is 4 Gm. initially and 1 Gm. every 6 hours thereafter by mouth for adults; and comparable doses on the basis of body weight for children. If parenteral therapy is required, 2–3.5 Gm. may be given each day intravenously to adults in divided doses, and comparable doses to children. Therapy should be continued until the temperature has been normal for five to seven days. If a relapse occurs, the patient should be treated with the same doses as were given for the original infection until the temperature again has remained within normal limits for several days. Chloramphenicol will not eliminate salmonellae from the stools of carriers, nor does it influence the frequency of intestinal perforation or hemorrhage.

Salmonella enteritis should be treated in the same manner as salmonella fever except that therapy need be continued only for two or three days after the diarrhea has subsided.

BRUCELLOSIS.—Although the tetracyclines and chloramphenicol are effective when given alone in this disease, the best results

are obtained and the fewest relapses occur when a tetracycline is combined with streptomycin. Doses of 0.5 Gm. of tetracycline at 6-hour intervals by mouth are given along with 1 Gm. of streptomycin or dihydrostreptomycin at 12-hour intervals. This therapy should be continued until the patient is essentially fever-free for three days. This usually necessitates 10 days or two weeks of treatment. If a relapse occurs, another identical course of therapy should be given.

RICKETTSIAL INFECTIONS.—These include Rocky Mountain spotted fever, flea-borne and louse-borne typhus fever, Q-fever and rickettsial pox. They may be treated with either tetracycline or chloramphenicol. The former may be given in doses of 2 Gm. initially, followed by 0.5 Gm. doses at 6-hour intervals. Chloramphenicol is given in an initial dose of 4 Gm., followed by 1 Gm. at 6-hour intervals. Treatment is continued until at least three days of practically normal temperature have passed. Relapses are treated in the same manner as the original infection.

In sector V are the viruses and fungi. Our present antibiotic weapons are useless against the viruses, with the exception of the psittacosis-lymphogranuloma group; and against the fungi, with the exception of actinomyces, nocardia and candida. The course of psittacosis and lymphogranuloma venereum is shortened by the use of one of the tetracyclines. The evidence for the value of the tetracyclines in primary atypical pneumonia is equivocal, but most authorities recommend its use at least in severely ill patients.

Most cases of actinomycosis will respond to penicillin or one of the tetracyclines. Penicillin, streptomycin or sulfadiazine may be successful in the treatment of nocardial infections.

The micro-organisms in sector II cause chronic infections. Recovery from these is slow. Resistant organisms appear and become predominant. In this sector the organisms often give trouble because strains appear that are resistant to many or all of the antibiotics. The bacteria involved are staphylococci, alpha and gamma streptococci, enterococci, pseudomonas, proteus, the coliforms, and tubercle bacilli. The problem of antibiotic-resistant bacteria will be considered later.

Sector I is inhabited by micro-organisms of low virulence that cause infection only because they are able to avoid the body

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defenses of the host by taking refuge in the swamps and thickets of lowered host resistance. These same refuges also protect them against antibiotics. By "swamps and thickets" is meant anatomic and physiologic defects of the host, such as bronchial asthma, bronchiectasis, ureteral calculi and strictures, prostatic hypertrophy, and so forth.

RESISTANCE TO ANTIBIOTICS

Let us now return to sector II and the problem of antibiotic-resistant bacteria. Resistant organisms may appear in patients as a result of (*1*) replacement of sensitive bacteria by resistant bacteria from outside the host, (*2*) by overgrowth of resistant bacteria of the same or of a different species that are already within the host, and (*3*) by mutation or adaptation of sensitive into resistant strains. For practical purposes we can combine numbers (*2*) and (*3*) because we are mostly concerned with whether the resistant organism has entered the patient from the outside or appeared from among the bacteria that were present at the start of therapy. The staphylococcus is a good example of the first type of organism. As shown in Figure 1, my colleagues and I (*1*) found that 51 per cent of the staphylococci obtained from the upper respiratory tracts of patients entering the hospital were resistant to penicillin. On the other hand, 85 per cent of staphylococci from the noses and throats of the personnel in the hospital were resistant. This, we believe, accounted for the fact that 88 per cent of the staphylococci from patients on discharge were resistant. After the patients had been at home for seven weeks, only 31 per cent of the staphylococci were resistant. This is almost exactly the percentage (32 per cent) of resistant staphylococci found in the upper respiratory tracts of household contacts.

The tubercle bacillus represents the second type of organism: during therapy, antibiotic-resistant forms of this organism appear from among bacteria that were present in the body of the host at the start of therapy. Cummings and Livings (*2*) found, for instance, that only 2.6 per cent of strains of Mycobacterium tuberculosis from patients who had had no previous streptomycin therapy were resistant to this antibiotic.

The prevention of the appearance of resistant strains will differ

for these two groups of organisms. The use of streptomycin and isoniazid or streptomycin and para-aminosalicylic acid will delay or prevent the appearance of resistant tubercle bacilli. This technique is not nearly so successful in the case of staphylococci. My associates and I (3) have shown that when cultures for staphy-

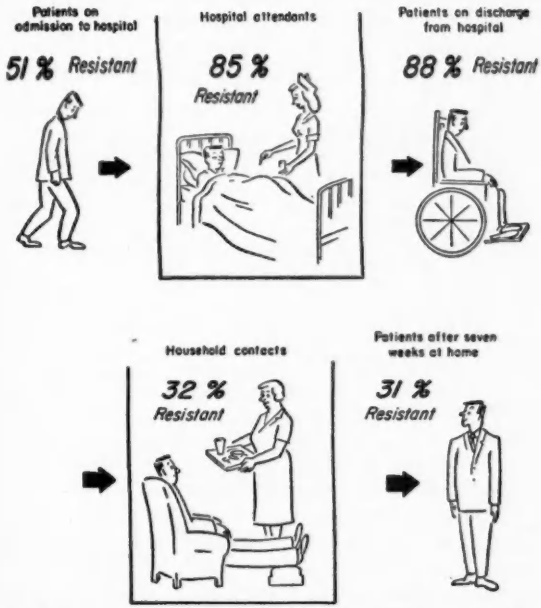

FIG. 1.—Percentage of penicillin-resistant micrococci cultured from upper respiratory tracts of patients, hospital attendants and household contacts. (Figs. 1 and 2 from Dowling, H. F., *et al.*: J.A.M.A. 157:327, 1955.)

lococci were taken from the noses and throats of patients on admission to our hospital and at intervals thereafter, if penicillin was used alone, 71 per cent of negative cultures remained negative; whereas if chlortetracycline was added to penicillin, 88 per cent of the cultures remained negative. Eventually, however, if the patient stayed in the hospital long enough, staphylococci

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usually appeared in his nose and throat, and these were resistant to both penicillin and chlortetracycline. Other measures must be used to prevent the appearance of resistant staphylococci. Spread of resistant staphylococci from patient to patient and from hospital personnel to patient should be prevented by proper aseptic techniques, especially in the case of susceptible individuals: young infants, patients with open wounds, postoperative patients, debili-

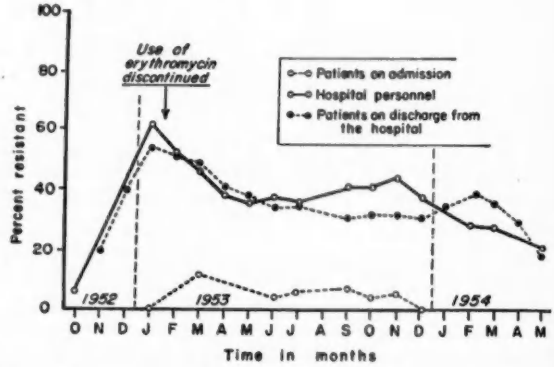

FIG. 2.—Percentage of erythromycin-resistant staphylococci cultured from upper respiratory tracts of patients and personnel of a hospital, October, 1952 to May, 1954 (three-month moving averages).

tated patients and other patients who are likely to develop pulmonary complications.

Is there any hope for the future? There are several indications that when an antibiotic is used less often, the percentage of resistant strains in the population falls. As shown in Figure 2, when erythromycin was introduced into our hospital in September, 1952, erythromycin-resistant staphylococci were not found in the upper respiratory tracts of the personnel of the hospital nor of patients on admission. Erythromycin-resistant strains soon appeared in the attendants and soon thereafter in the patients, reaching a peak in January after four months of use. Erythromycin therapy was discontinued in January, except in a very occasional case, and the percentage of erythromycin-resistant

strains fell to approximately 20 per cent in the ensuing 16 months. Low percentages of erythromycin-resistant staphylococci appeared in patients on admission from March through November, 1953, as a result of the use of erythromycin outside the hospital.

Other evidence of the diminution of the number of antibiotic-resistant strains is available. Kirby and Ahern (4) found that the percentage of strains of staphylococci resistant to chloramphenicol obtained from their patients fell from 20 per cent to 6 per cent over a period of one year, after the use of chloramphenicol had been curtailed on their wards. Finland (5) reported a decrease in the percentage of strains of gonococci resistant to sulfadiazine in 1954 as compared to 1949. This was undoubtedly due to the less frequent use of the sulfonamides in the treatment of gonorrhea during the intervening years. As additional antibiotics, such as streptonivicin and cathomycin come into use, the rate of disappearance of penicillin-, tetracycline- and chloramphenicol-resistant staphylococci from the population should be accelerated.

As shown in Table 1, certain groups of antibiotics exhibit cross-resistance. In other words, when a certain micro-organism is resistant to one of these antibiotics, it is resistant to the other antibiotics in the group also. Streptomycin and dihydrostreptomycin behave alike with respect to bacteria and exhibit cross-resistance with neomycin and streptothrycin also. Tetracycline and its two analogues act similarly upon micro-organisms, and sometimes exhibit cross-resistance to chloramphenicol. Erythromycin and carbomycin act identically upon micro-organisms, as do streptonivicin and cathomycin. There is no point, therefore, in changing to another antibiotic of the same group if the patient's infecting organism has already been shown to be resistant to one of the other antibiotics in the group.

ENDOCARDITIS CAUSED BY NON-HEMOLYTIC STREPTOCOCCI (SUBACUTE BACTERIAL ENDOCARDITIS).—Most group D streptococci (enterococci) are at least partially resistant to the known antibiotics. Alpha and gamma streptococci that are not enterococci are sometimes resistant to one or more of the antibiotics. Occasionally, resistant forms have been observed to appear during the course of penicillin therapy and frequently during the course of therapy with one of the tetracyclines or erythromycin.

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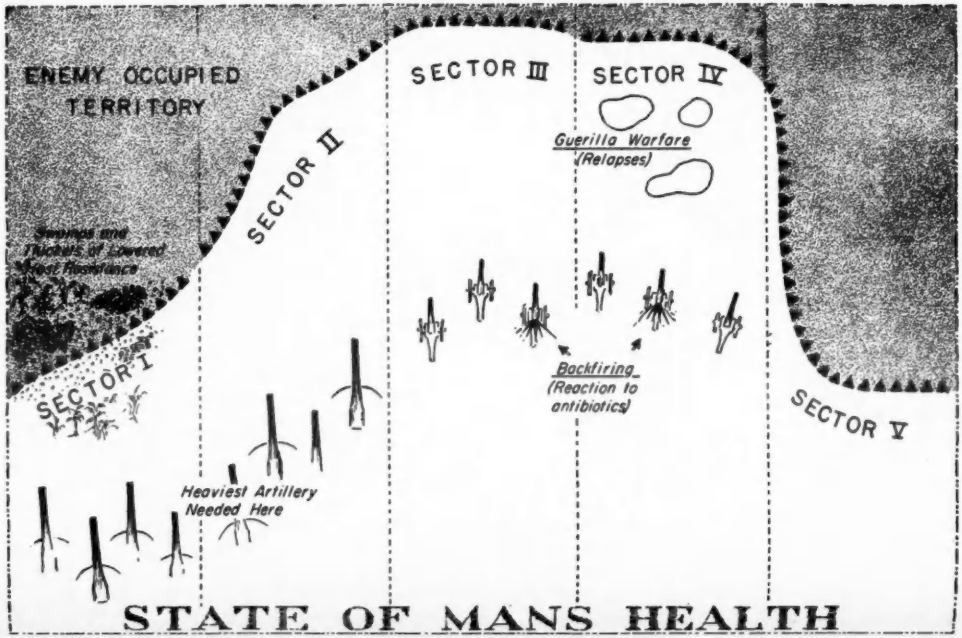

FIG. 3.—*Sector I:* chronic bacterial infections characterized by anatomic and/or physiologic defects in the host. (A) Usually mixed infections. (B) Many of the organisms are of low virulence in ordinary circumstances. (C) Involve especially the areas which communicate with the outside: (a) skin and subcutaneous tissue, (b)

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FIG. 3.—*Sector I:* chronic bacterial infections characterized by anatomic and/or physiologic defects in the host. (A) Usually mixed infections. (B) Many of the organisms are of low virulence in ordinary circumstances. (C) Involve especially the areas which communicate with the outside: (a) skin and subcutaneous tissue, (b) respiratory tract, (c) genitourinary tract. *Sector II:* chronic bacterial infections associated with appearance of antibiotic-resistant strains. (A) Staphylococcic infections. (B) Alpha and gamma streptococcic infections. (C) Streptococcus faecalis infections. (D) Infections caused by Pseudomonas, Proteus and coliform organisms. (E) Tuberculosis. *Sector III:* bacterial infections which yield promptly to antibiotic therapy. Infections caused by: pneumococci, beta streptococci, meningococci, B. anthracis, P. tularensis, P. pestis, H. influenzae, H. pertussis, shigellae, treponemes. *Sector IV:* infections which yield promptly to antibiotic therapy but sometimes relapse. (A) Typhoid and other salmonella infections. (B) Brucellosis. (C) Rickettsial diseases. *Sector V:* diseases caused by viruses, yeasts and fungi: psittacosis, lymphogranuloma venereum, trachoma, primary atypical pneumonia (?), other viral diseases, actinomycosis, nocardiosis, diseases caused by other yeasts and fungi. (From Dowling, H. F.: Antibiotics & Chemother. 5:13, 1955.)

In the case of endocarditis caused by a penicillin-sensitive organism belonging to one of these groups, penicillin alone may be administered for from four to six weeks. The best therapy, however, is a combination of penicillin and streptomycin. The former is given in doses of 600,000 units of aqueous procaine penicillin or crystalline penicillin G at 6-hour intervals for two weeks. Streptomycin or, probably better still, equal parts of streptomycin and dihydrostreptomycin are given in doses of 2 Gm. a day for the first week and 1 Gm. a day for the second week. By this method of therapy an 80 per cent cure rate, or better, can be attained.

Patients with endocarditis caused by streptococci that are relatively resistant to penicillin should be treated with a combination of penicillin and streptomycin. In our clinic we use 10,000,000–20,000,000 units a day of penicillin (plus 2 Gm. of probenecid; or twice that dose without probenecid) and 2 Gm. of streptomycin a day for six weeks. Approximately 60-70 per cent of patients with endocarditis caused by penicillin-resistant streptococci can be saved by such a regimen.

STAPHYLOCOCCIC INFECTIONS.—Mild staphylococcic infections, such as furuncles and subcutaneous abscesses, usually respond to procaine penicillin in doses of 300,000 units a day. Staphylococcic sinusitis may also improve rapidly on this regimen, providing drainage from the sinuses is satisfactory.

If the staphylococcic infection is more widespread, if remote structures, such as the pleura, the joints, the meninges or the endocardium, are involved or if therapy with one or more antibiotics has already been unsuccessful, the organisms should be tested for sensitivity to penicillin, tetracycline, chloramphenicol, erythromycin and streptonivicin or cathomycin, preferably by the tube-dilution method.

Penicillin will be the drug of choice if the organism shows sensitivity to it. If growth is inhibited by 0.5 unit of penicillin per cc. (or less), the drug should be given for six weeks in doses of 2,400,000 units a day. If between 0.5 and 4 units of penicillin per cc. is required for inhibition of growth, from 10,000,000 to 80,000,000 units of penicillin a day should be given (or one-half of these amounts if accompanied by 2 Gm. of probenecid a day).

If the causative organism is inhibited by less than 1 unit per cc.

of tetracycline or less than 2 units per cc. of chloramphenicol and resistant to more than 4 units of penicillin per cc., tetracycline or chloramphenicol may be given.

With the introduction of streptonivicin and cathomycin, a new group of antibiotics is available which may be used in cases in which staphylococci are resistant to the other antibiotics. Doses up to 40 mg. per kilogram of body weight per day have been given in serious staphylococcic infections. These doses are given orally at 6-hour intervals.

If any of the foregoing regimens fail to bring about a fall in temperature and improvement in symptoms within 10 days or two weeks, a change may be made to one of the other regimens if indicated by sensitivity tests; or a combination of maximal doses of penicillin and intravenous tetracycline may be tried. Another alternative would be to give bacitracin. Unfortunately, even when the most suitable regimen is used, half of the patients still die. Nevertheless, prompt and adequate treatment can save the lives of the other half.

URINARY INFECTIONS.—Patients with acute infections of the urinary tract often recover spontaneously without any treatment other than rest and ingestion of large quantities of fluid. It is unwise, therefore, to treat these infections immediately with antibiotics, especially since such therapy is likely to be followed by the appearance of organisms that are resistant to the antibiotic used. It is suggested, therefore, that these infections be treated with sulfonamides (sulfadiazine, sulfisoxazole or triple sulfonamides). An initial dose of 2–4 Gm. should be given, followed by 1 Gm. at 4-hour intervals. Sulfonamide therapy should be accompanied by sufficient intake of fluids to assure the excretion of at least 2–3 liters of urine a day.

If the infection does not clear on a week of this therapy, or if improvement is followed by relapse, the entire problem should be reexamined. A search should be made for anatomic defects of the urinary tract, such as renal calculi, abnormal calicyes, hydroureter, polycystic kidney, ureteral or urethral stricture, prolapse of the bladder or prostatic hypertrophy. At the same time, the urine should be cultured and the organisms that are obtained should be tested carefully for their sensitivity to streptomycin, tetracycline, chloramphenicol and polymyxin. This

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should preferably be done more than once. If the anatomic defect is one that can be removed, this should be done under cover of proper antibiotic therapy as dictated by the in vitro tests. If the defect cannot be corrected, a short course of the proper antibiotic should be given, and in the meantime the patient's general condition should be improved as much as possible, and he or she should be made ambulatory if this can be done. By this method, the infection may be suppressed sufficiently so that the patient's own resistance will do the rest. Especially should inlying catheters be removed as soon as possible, and periodic catheterizations performed as infrequently as possible, and then only with meticulously sterile technic. If long-continued therapy is needed, it is best to use sulfonamides in regular doses, as given above, or small doses of tetracycline (0.5 Gm. twice a day). The purpose of this therapy is to suppress the infection somewhat, without eliminating all of one kind of organism completely and thus changing the flora to a species that is not affected by any of the antibiotics.

MIXED INFECTIONS

Let us now move over to sector I of Figure 3, where mixed infections prevail, usually along with lowered host resistance. This sector is widening all the time. As more and more people survive the acute infections, they survive with a residual chronic infection, or with residual defects that invite infections by organisms that are of low virulence; or they live into the age where their vitality is lowered and they become an easy prey to bacteria. These mixed infections are usually in the skin and subcutaneous tissues, in the respiratory tract or in the genitourinary tract. We may therefore use a mixed infection of the bronchial tree as an example.

CHRONIC BRONCHOPULMONARY INFECTIONS.—When a patient with chronic bronchiectasis is seen in an acute exacerbation or when, because of complications such as heart disease, it is imperative that his condition be improved promptly, a large dose of a broad spectrum antibiotic is the ideal therapeutic agent. In our clinic, we have been able to bring about a reduction in fever, pulmonary signs and evidences of toxicity by the use of 0.5 Gm.

of tetracycline intravenously at 8-hour intervals for five days. The most pronounced effect is on the sputum, which loses its purulent character and is decreased to at least one-half its former volume or sometimes disappears altogether.

The long-continued care of these patients is more difficult. Antibiotics, whether given singly or in combination, will only displace the prevailing bacteria by others that are resistant to the antibiotic that is being administered, until finally the bacterial flora will be resistant to all the available antibiotics. Combinations of antibiotics are not the answer here. My co-workers and I (6) have studied the tracheal flora in 72 tracheotomized patients with poliomyelitis. A single wide-range antibiotic (such as tetracycline or chloramphenicol) was more effective than any other antibiotic combination in preventing the implantation of bacteria. However, none of the antibiotics, singly or in combination, were able to decrease or eliminate tracheal flora, once they had become established, any better than purely symptomatic therapy. Three or more antibiotics, given concomitantly, decreased the number of species present better than antibiotics given singly or in combinations of two, but not significantly more than symptomatic therapy alone. When three or more antibiotics were used, moreover, *candida* grew five times more frequently than in patients treated symptomatically.

The lesson is clear. Unless we are careful, in chronic mixed infections we can do more harm than good by the use of antibiotics. If bronchiectasis is present and amenable to surgery, the patient should be prepared for this by several days of intravenous tetracycline therapy, or by other antibiotics if they are indicated instead, and the affected lobes removed. Many patients are not so fortunate, and their management consists only of symptomatic measures and a delaying action. Intravenous therapy is continued for five days, and if improvement is not sufficient, the dose is increased to 0.5 Gm. at 6-hour intervals for an additional five days. Comparable doses on the basis of body weight are given to children. Chloramphenicol may be given instead of tetracycline. This has the advantage that it may be given by mouth and the disadvantage that blood dyscrasias occasionally occur. The dose is 2–4 Gm. initially, followed by 1 Gm. at 6-hour intervals in the case of adults; children are given

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comparable doses determined on the basis of the body weight.

The patient may remain relatively free from infection for weeks or months, until the next upper respiratory infection sets the whole chain of events in motion again; or the sputum may gradually return to the previous purulent state over the course of the next several weeks.

If the patient does not respond to this therapy, the bacteria in the sputum should be tested for sensitivity to penicillin, streptomycin, tetracycline, chloramphenicol and polymyxin. If an organism that is present in large numbers is sensitive to one of the other antibiotics, that should be used. Penicillin may be given by inhalation, although in our clinic we see no advantage to this and prefer the intramuscular route. Doses of 600,000 units of aqueous procaine penicillin should be given at 12–24-hour intervals. Polymyxin should be given by inhalation, however, since renal damage has not been known to occur when this route was used.

In the exacerbations of chronic bronchiectasis, chronic bronchitis, emphysema and bronchial asthma, it is most important that the proper systemic measures be employed along with the antibiotics. Bronchodilators, such as aminophylline and epinephrine and its analogues, should be used to improve aeration and drainage as much as possible. Iodides are also helpful in some cases. Oxygen therapy by catheter, tent or, preferably, in some cases at least, by mask and under positive pressure, is often a *sine qua non*.

Solitary lung abscesses usually respond to 300,000–600,000 units of aqueous procaine penicillin a day, or to 0.5 Gm. of tetracycline at 6-hour intervals. Postural drainage should be employed as long as needed.

When a bronchiectatic condition is sufficiently localized to be amenable to surgery and the pulmonary reserve is adequate, the patient should be treated with the proper antibiotic; and when the infection has been brought under the best possible control, the affected portions of the lungs should be removed. This is also the proper procedure when a lung abscess fails to heal on a medical regimen. It is important not to use full therapeutic doses of antibiotics except for a short period of time during acute episodes. On the other hand, tetracycline orally in

doses of 250 mg. twice a day, as McVay and Sprunt (7) showed with chlortetracycline, should decrease the number of acute exacerbations.

USE OF COMBINATIONS OF ANTIBIOTICS

In certain infections, the value of combinations of antibiotics has been proved, in both the laboratory and the clinic. The use of penicillin plus streptomycin in endocarditis caused by penicillin-sensitive and penicillin-resistant streptococci has already been discussed. Streptomycin plus one of the tetracyclines represents optimal therapy in brucellosis. Occasionally, a combination of penicillin plus one of the tetracyclines or chloramphenicol will be effective in a serious infection caused by staphylococci that are resistant in vitro to each of these drugs when used alone. This situation should be determined, if possible, by in vitro tests before the combination is used. Combinations of streptomycin and isoniazid or para-aminosalicylic acid will delay the appearance of resistant strains of tubercle bacilli. In our clinic we have also used a combination of erythromycin and chloramphenicol in infections caused by staphylococci resistant to other antibiotics, in order to delay the appearance of organisms resistant to erythromycin or chloramphenicol.

If the infection does not fall into any of the above groups, combinations of antibiotics are not recommended, unless the infection is a mixed one and a single antibiotic will not be effective against the different bacteria. The administration of more than one antibiotic when one is sufficient merely obscures the therapeutic picture and increases the possibility of untoward reactions.

UNTOWARD REACTIONS TO ANTIBIOTICS

In Figure 3 some of the guns are portrayed as "back-firing." These represent the untoward reactions resulting from antibiotics and listed in Table 3. Such reactions are undoubtedly increasing all the time as a result of promiscuous use of antibiotics. Local reactions occur to all of the antibiotics. When antibiotics are given orally, any of them may cause nausea

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and/or diarrhea, but chlortetracycline and oxytetracycline are more likely to do so, tetracycline and chloramphenicol less likely, and penicillin, erythromycin and streptonivicin rarely. Repository injections of penicillin will cause some local pain, as will intramuscular injections of the tetracyclines and chloramphenicol. Injections into the cerebrospinal fluid often produce meningeal irritation and may cause myelitis. Intravenous injections of the tetracyclines and chloramphenicol will also cause phlebitis if the same vein is used over a period of several days. These inflammations will heal within a short time after administration of the antibiotic has been discontinued. Penicillin will cause convulsions if applied directly to the cerebral cortex.

TABLE 3.—Adverse Effects of Antibiotic Administration

1. Local reactions	4. Alterations in bacteria
2. Hypersensitivity reactions	*a*) Appearance of resistant organisms
3. Drug toxicity	*b*) Changes in flora
	5. Mistakes in diagnosis

In general, local reactions either are preventable or can be obviated or minimized by proper administration and safeguards.

The second group of untoward reactions, however, seems to be on the increase. Von Oettigen (8) found a total of 83 severe and 46 fatal anaphylactoid reactions after administration of penicillin reported in the literature. Such reactions were rarely observed following the administration of other antibiotics. Other types of hypersensitivity reactions are much more frequently observed, especially when penicillin is used. Hypersensitivity reactions are most frequent in patients who are allergic; in patients who have received the same antibiotics before, especially if they had a reaction the first time; in patients who receive large doses, and in patients who are under treatment for a long period of time. There is some evidence that the procaine preparations of penicillin are more likely to be followed by hypersensitivity reactions than penicillin G in comparable doses. Many of these reactions may be prevented by inquiring whether the patient has had the antibiotic before and, if so, whether he had a reaction; by skin testing all doubtful cases before giving the first dose; by giving sufficiently large doses of the anti-

biotic to achieve the desired result promptly; by discontinuing antibiotic therapy as soon as the desired result has been accomplished, and, above all, by refraining from administering antibiotics when they are not indicated. Since death has followed an intracutaneous test with penicillin, skin tests should be done by the scratch method, using a 1:1,000 dilution of the antibiotic. Patients who are hypersensitive to penicillin G may or may not be hypersensitive to other preparations of penicillin, such as penicillin O or penicillin V.

Direct toxic effects of antibiotics upon certain organs are often seen. If streptomycin is used for a long period of time, damage to the eighth nerve invariably occurs, usually producing vertigo but sometimes deafness. Dihydrostreptomycin, on the other hand, is more likely to cause deafness. Both of these phenomena may be prevented to some extent by using a combination of equal parts of streptomycin and dihydrostreptomycin.

If chlortetracycline is used intravenously in amounts far exceeding therapeutic doses, fatty infiltration of the liver is sometimes observed. Since this does not occur during oral therapy and with proper therapeutic doses given intravenously, it is not a contraindication to the use of chlortetracycline.

Aplastic anemia and agranulocytosis have been observed following the use of chloramphenicol. For this reason chloramphenicol therapy is not advised when another antibiotic is available that will be just as effective. When its use is justified, however, chloramphenicol should be used and frequent blood counts performed. If anemia or leukopenia are observed, administration of chloramphenicol should be discontinued immediately. In our hands, no serious results have occurred when this procedure has been followed.

Bacitracin and polymyxin both produce renal irritation. Although there is no proof that permanent damage to the kidneys has followed their administration, it seems wisest to limit their use to severe infections in which other antibiotics have not been successful.

The appearance of resistant organisms has already been considered. Another kind of untoward reaction is overgrowth of the original flora by an organism that was present only in small numbers or not present at all at the beginning of therapy. Figure

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4 shows the micro-organisms that commonly cause such superinfections in different areas of the body. In the middle ear, pseudomonas and staphylococcus most often cause superinfections; on the tongue, fungi; in the throat, larynx and bronchi, staphylococcus and the coliforms. In the lungs, any one of a number of micro-organisms may cause superinfection: staphylococcus, the coliforms, H. influenzae, fungi, proteus and pseudomonas. In the intestines, staphylococcus, pseudomonas or proteus may cause superinfection. Monilia may cause proctitis or vaginitis. In the urinary tract, coliforms, pseudomonas, proteus, staphylococcus or enterococcus may displace other organisms.

Certain facts stand out when superinfections develop. They are most likely to occur in patients who are weakened and debilitated, in the very young and the very old and in postoperative patients. They are more likely to follow the prolonged use of an antibiotic, especially if large doses have been administered. They are much more common when the broad spectrum antibiotics are employed or when two or more antibiotics are given concurrently. The reason for this is that no matter how broad the field of action of the antibiotics or no matter how many antibiotics are used, there are always some micro-organisms that are not inhibited. These remaining organisms grow profusely because they no longer have to compete with other micro-organisms for their nutritional requirements.

The most talked-of superinfection is the staphylococcic enteritis that sometimes follows the use of oxytetracycline or, less frequently, one of the other tetracyclines. Many of the cases of diarrhea that are attributed to these drugs are undoubtedly due to something else. Enterocolitis following surgery was observed long before antibiotics were discovered, and some of the cases undoubtedly belong in this category. The etiology is unknown. Many of the cases of diarrhea are probably due to simple irritation by the antibiotic. The diarrhea is sometimes mild enough so that administration of the antibiotics need not be stopped. In other cases, it is severe and may continue for days or even weeks. A few cases are due to infection with staphylococci. Pure cultures of staphylococci are obtained from the stools, and staphylococcic abscesses are found in the wall of the intestines at autopsy.

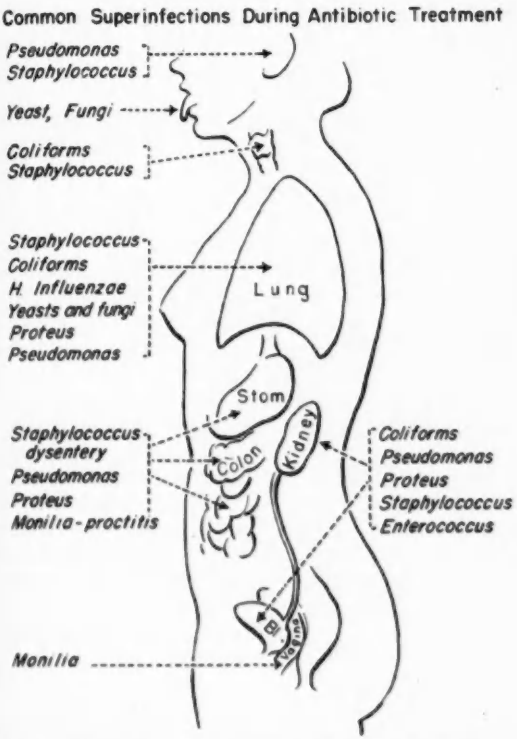

FIG. 4.—Superinfections from antibiotic therapy. (From Jackson, G. G., and Dowling, H. F.: GP 8:34, 1953.)

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When diarrhea appears, the administration of antibiotics should be discontinued unless the diarrhea is mild and further administration is imperative. Usually the diarrhea disappears within a few hours or days without further treatment. If the diarrhea is severe, Gram stains should be made of the feces; and if staphylococci are found to predominate, erythromycin in doses of 0.5 Gm. at 6-hour intervals should be administered promptly and continued until two or three days after the diarrhea has stopped.

Mistakes in diagnosis have been listed under the adverse effects of antibiotic administration in Table 3 because of the all-too-common practice of giving antibiotics first and diagnosing afterward. This is poor practice for two reasons. First, the diagnosis of a noninfectious condition is sometimes missed by this method until it is too late. A patient with fever may have pulmonary infarcts instead of an infection in the lung. The prompt institution of anticoagulant therapy may save his life, whereas two to three weeks of futile antibiotic therapy not only is expensive but may set the stage for a fatal embolus. Or, in the case of a malignancy, so much time may be wasted in shifting from one antibiotic to another in an attempt to cure a non-existent infection that the time for complete removal of the tumor may have passed. A second reason why this is not good practice is that doctors tend to become careless in making diagnoses if in one major class of illnesses, such as the infections, they do not exercise their skills.

PROPHYLACTIC USE OF ANTIBIOTICS

One more fact is obvious from the diagram of the battle-front: in none of the sectors have we pushed the enemy-microbes out of Man's life altogether. Prophylaxis with antibiotics is sometimes effective, however, when directed against the organisms in sector III. Gonococcic infections can be prevented by the use of penicillin, and meningococci can be eliminated from a family or a community by the prophylactic administration of sulfadiazine, but our greatest successes have come in the infections caused by beta hemolytic streptococci. Miller and his associates (9) reported that among 77 children who had previously had rheumatic fever and who were given 200,000 units of penicillin

G by mouth twice a day, only 6.5 per cent had group A streptococcic infections during 2,040 patient-weeks of observation. This is in contrast to 37 per cent group A streptococcic infections among 94 siblings of the first group who received no antibiotics during 2,067 patient-weeks of observation. Thousands of attacks of rheumatic fever have been prevented by the prophylactic use of the sulfonamides or penicillin. The latter is preferred because resistant strains of group A streptococci have not been encountered in patients. If possible, every person who has had an attack of rheumatic fever should receive continuous penicillin prophylaxis until he is 21 years of age or for five years after the last episode of acute rheumatic fever, whichever is the later.

Oral penicillin is recommended in doses of 200,000 units twice a day, or benzathine penicillin may be given in doses of 1,200,000 units once every 28 days by the intramuscular route.

USE OF ANTIBIOTICS WITH HORMONES

The dramatic action of the corticosteroids and adrenocorticotropin (ACTH) in reducing the symptoms and signs of infectious processes has opened the tempting possibility to physicians that these substances may be beneficial in overcoming infections themselves. There is much experimental evidence to the contrary, however. For instance, cortisone has been shown to enhance infections caused by a number of micro-organisms, among which are streptococci, pneumococci, staphylococci, brucellae, typhoid bacilli, spirochetes, corynybacteriae, malaria parasites, trypanosomes, several varieties of fungi and the viruses of poliomyelitis and influenza (10). This is thought to be caused, at least in part, by the suppression of the local inflammatory reaction, with the result that micro-organisms are not held in check but are allowed to enter the blood stream and penetrate the tissues of the host with little hindrance. Clinically, it has been observed that a number of patients developed tuberculosis while receiving corticosteroid therapy, although there had been no evidence of infection before therapy.

On the other side of the picture, adrenal insufficiency has long been known to increase the susceptibility of the host to infection. The increased vulnerability of the patient with Ad-

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dison's disease is the best example of this. It has been shown that adrenalectomized rats succumb rapidly to pneumococcic infection and that small doses of cortisone increase their resistance. Larger doses of cortisone, however, worsen the infection again. Cortisone also counteracts the effects of endotoxins upon the host. This is especially true of the shocklike state produced by the endotoxins of the gram-negative bacteria.

In the face of this dilemma, what is the clinician to do? The evidence seems to be overwhelming that these hormones should not be employed in infections caused by gram-positive bacteria, tubercle bacilli, fungi and viruses. In such infections, the hormones merely mask the infection, which all the while is proceeding at an accelerated pace. Kass and his associates (12) showed, for instance, that patients with pneumococcic pneumonia appeared to be clinically improved after having been placed on ACTH therapy, while at the same time the bacteremia continued.

Patients with overwhelming infections caused by gram-negative bacteria, in whom vasomotor collapse has occurred, may be benefited by treatment with cortisone or ACTH. Full doses of the proper antibiotics should be given at the same time and continued after hormone therapy has been stopped, until it is certain that the patient has recovered completely. The patient should be observed carefully, and frequent blood cultures should be made. Hormone therapy should be discontinued as soon as practicable.

When the Waterhouse-Friderichsen syndrome appears during the course of a meningococcic infection, full doses of a sulfonamide and of penicillin may be given and, along with these, hydrocortisone in doses of 300 mg. initially and 200 mg. at 12-hour intervals by the intravenous route. Vasomotor collapse should also be combated by the intravenous administration of norepinephrine. By vigorous treatment of this kind, a few patients have undoubtedly been saved who would otherwise have succumbed to this infection.

SUMMARY

In summary, the attack upon pathogenic micro-organisms must be threefold: (*1*) Prophylactic administration, when possible,

to eliminate micro-organisms before they invade the State of Man's Health; (*2*) skilful therapeutic use of antibiotics when micro-organisms have already produced a disease—skilful in that the proper antibiotic or combination of antibiotics should be used, in proper dosage, for a sufficient length of time to rout the enemy, and (*3*) prevention of untoward reactions by refraining from using antibiotics when they are unnecessary and discontinuing their administration promptly when they are no longer needed.

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